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LOW SODIUM DIET PROTECTS FROM ALDOSTERONE-INDUCED ENDOTHELIAL DYSFUCNTION AND LEFT VENTRICULAR HYPERTROPHY IN SUBJECTS WITH RESISTANT HYPERTENSION

Mari K. Nishizaka, Monique N. Pratt-Ubunama, David A. Calhoun. Vascular Biology and Hypertension Program, University of Alabama at Birmingham, Birmingham, AL.

Experimental models have demonstrated that aldosterone-induced cardiovascular damage requires concomitant high dietary sodium exposure. Studies from this and other laboratories have linked aldosteronism to endothelial dysfunction and left ventricular (LV) hypertrophy in human subjects. The current study was designed to determine if low sodium intake can blunt aldosterone-induced endothelial dysfunction and LV hypertrophy (LVH).

Consecutive subjects (n=155) with resistant hypertension were prospectively evaluated with an early morning plasma aldosterone, renin and 24-hr urinary aldosterone and sodium. Changes in brachial artery diameter during hyperemia (flow-mediated dilation or FMD) were measured as an index for endothelial function. FMD was negatively correlated and LV end-diastolic diameter (LVDD) and LV mass (LVM) were positively correlated with aldosterone excretion ($r=0.38$, $p<0.0001$ and $r=0.26$, $p=0.004$). However the product of 24-hr sodium and aldosterone was an even stronger predictor of FMD and LVH than aldosterone alone (FMD: $r=-0.59$, $p<0.0001$, LVM: $r=0.35$, $p<0.0001$). Among subjects with high aldosterone excretion ($>$ 12 μg/24-hr), low dietary sodium ingestion ($<$100 meq/24-hr) was associated with significantly less endothelial dysfunction and significantly less LVH. Three-month treatment with spironolactone significantly increased FMD and decreased LVH in subjects with and without aldosteronism, independent of blood pressure reduction level. However, these improvements were significantly greater in subjects with a high aldosterone and sodium excretion.

These results are the first demonstration that low dietary sodium ingestion can protect from aldosterone-induced vascular and ventricular dysfunction in humans. Further, these results suggest that cardiovascular risk in subjects with resistant hypertension may be predicted by the product of urinary aldosterone and sodium excretion.

Key Words: Aldosterone-Salt, Left Ventricular Hypertrophy and Endothelial Dysfunction, Resistant Hypertension

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CHANGES IN PLASMA RENIN MATCH THE ANTIHYPERTENSIVE EFFECTS OF ALISKIREN IN PATIENTS WITH HYPERTENSION: PLACEBO/ IRBESARTAN-CONTROLLED TRIAL WITH THE ORALLY ACTIVE RENIN INHIBITOR ALISKIREN

Juerg Nussberger, Alan H Gradman, Roland E Schmieder, Robert L Lins, William B White, Margaret Prescott, Yanntong Chiang. Hypertension & Vascular Medicine, CHUV, Lausanne, Switzerland.

For several decades, the lack of oral availability and poor antihypertensive effects of renin inhibitors (RI), despite seemingly powerful inhibition of conventionally measured plasma renin activity (PRA), have discredited RI as cardiovascular drugs. Aliskiren is a novel orally effective RI with antihypertensive potency comparable to losartan or irbesartan. The present study investigated the effects of aliskiren and irbesartan on PRA, measured by the reliable antibody trapping technique, as well as on plasma active renin concentration (ARC) and sitting systolic blood pressure (SBP).

In 569 patients with mild to moderate hypertension (baseline sphygmomanometric sitting blood pressure 152±12/99±4 mmHg, mean±SD), PRA and ARC, as well as SBP were measured before and after 8 weeks of treatment with once daily oral doses of aliskiren (150, 300 or 600mg), irbesartan 150mg or placebo. The effects of study treatments on PRA, ARC and SBP are summarized in the Table.

Aliskiren reduced PRA by 69%, 71% and 75% at 150, 300 and 600mg respectively, while irbesartan doubled PRA. Most of the antihypertensive effect of aliskiren was obtained with the lowest dose, but higher doses slightly further decreased SBP. Aliskiren 150mg and irbesartan 150mg provided similar increases in ARC and hence comparably blocked the renin-angiotensin system (RAS), and the achieved SBP was also the same. Aliskiren 300mg and 600mg caused greater increases in ARC compared with irbesartan 150mg ($p<0.05$), and further decreases in SBP. The dose-dependent increases in ARC observed with aliskiren document increasing blockade of the RAS.

In conclusion, aliskiren provides a parallel reduction in PRA and SBP, a dose-dependent blockade of the RAS and is at least as effective as irbesartan at comparable dosages (150mg).

Treatment	N	PRA (ng/mL/h)		ARC (pg/mL)		SBP (mmHg)	
		Baseline	Week 8	Baseline	Week 8	Baseline	Week 8
Placebo	111	0.72	0.64	6.2	5.6	152 ± 12	147 ± 18
Aliskiren 150mg	112	0.66	0.20	6.0	15.3	151 ± 11	140 ± 14
Aliskiren 300mg	115	0.59	0.17	6.1	21.0	152 ± 10	137 ± 14
Aliskiren 600mg	113	0.64	0.16	5.8	34.9	153 ± 12	137 ± 16
Irbesartan 150mg	118	0.64	1.33	5.5	11.3	153 ± 11	140 ± 16

PRA and ARC values are geometric means; SBP values are mean ± SD

Key Words: Hypertension, Plasma Renin Activity, Renin Inhibitor

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EFFECT OF NAD(P)H OXIDASE INHIBITION ON ANGIOTENSIN II-STIMULATED COLLAGEN PRODUCTION IN ADULT RAT CARDIAC FIBROBLASTS

Italia Papparella, Giulio Ceolotto, Victor Petrov, Robert Fagard, Andrea Semplicini, Paul Lijnen. Hypertension Unit, Katholieke Universiteit Leuven (K.U.Leuven), Leuven, Vlaams Brabant, Belgium; Department of Clinical and Experimental Medecine, University of Padova, Padova, Italy.

The aim of this study was to determine whether NAD(P)H oxidase-inhibition could affect the soluble collagen production in control and angiotensin II-stimulated cardiac fibroblasts. Cardiac fibroblasts from passage 2 from normal male adult rats (n= 4-6) were cultured to confluency and incubated in serum- and phenol red-free Dulbecco's modified Eagle's medium for 24 h. The cells were preincubated wth(out) apocynin (100 μmol/l) or diphenylene iodonium chloride (DPI, 1 μmol/l) for 1 h and further incubated with(out) angiotensin II (1 μmol/l) for 24 h in this medium. Soluble total collagen production was measured spectrophotometrically with picrosirius red as dye (Sircol assay) or by tritium-proline incorporation. Angiotensin II increased ($p<0.01$) the soluble collagen production in cardiac fibroblasts by 88.5 ± 24.0(SEM) %. Apocynin, which inhibits the association of p47phox and p67phox with gp91phox within the membrane NAD(P)H oxidase complex, completely ($p<0.01$) blocked the angiotensin II-stimulated collagen production. Apocynin had however no effect on the collagen production in control fibroblasts. DPI, a cytosolic flavoprotein inhibitor of NAD(P)H oxidase, completely blocked ($p<0.01$) the angiotensin II-stimulated collagen production, but did not affect the basal collagen production. The collagen production assessed as tritium-proline incorporation was also increased ($p<0.01$) by angiotensin II, on average by 92.8 ± 7.4 %. Apocynin and DPI also blocked ($p<0.01$ and 0.05, respectively) the angiotensin II-stimulated tritium-proline incorporation but had no effect on the tritium-proline incorporation in control cardiac fibroblasts. Our data show that inhibition of the membrane-associated NAD(P)H oxidase complex with apocynin and DPI blocks the angiotensin II-stimulated collagen production in adult rat cardiac fibroblasts.

Key Words: Angiotensin II, Cardiac Fibroblasts, Collagen